UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,111	09/19/2005	Stephen D. Goble	21265P	1251

210 7590 09/24/2007

MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
HABTE, KAHSAY	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
09/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,111	GOBLE ET AL.	
	Examiner	Art Unit	
	Kahsay Habte	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *5-9,14-16,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,10-13,17-19 and 22-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/19/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-37 are pending in this application.

Election/Restriction

2. Applicant's election with traverse of Group II (benzoxazines, B = O and X = A = D = carbon) is acknowledged. The traversal is on the ground that "the compounds share a technical relationship, because the compounds have a common structural feature defined by Formula I in claim 1". The examiner disagrees with applicant's argument. As set forth in the restriction requirement, the special technical features of Groups I-VI are different one from the other. Note that the only technical feature that is common to the groups is the cyclopentyl ring. This is a small portion of the technical feature of the invention. The right hand side ring with four variables X, A, B and D is the bigger portion that plays role in defining the technical feature of Groups I-VI.

Applicants also argue that "the PCT examiner did not find that there was a lack of unity of invention". This is not found persuasive because the United Sates Patent and Trademark Office is *not* bound by the lack of unity determination by another International Searching Authority. MPEP 1875 states that whether or not the question of unity of invention has been raised by the International Searching Authority, it may be considered by the examiner when serving as an authorized officer of the International Preliminary Examining Authority. Thus, the Examiner is *not* bound by any previous determination made. In addition, 37 C.F.R. 1.484 indicates that the international preliminary examination is a non-binding opinion. Finally, 37 C.F.R. 1.499 states that, if

the Examiner finds that a national stage application lacks unity of invention under 37 C.F.R. 1.475, the Examiner may in an Office action require the applicant in the response to that action to elect the invention to which the claims shall be restricted. Thus, the determination of lack of unity is proper under the PCT treaty.

The requirement is still deemed proper and is therefore made FINAL.

Claims 5-9, 14-16 and 20-21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

3. The claims are drawn to multiple inventions for reasons set forth in the restriction requirement. The claims are examined only to the extent that they read on the elected invention. Cancellation of the non-elected subject matter is recommended in response to this Office Action. Applicants have to delete non-elected subject matter from the claims. For example in claim 1, applicants have to delete A = NR^8 and O, B = CR^2R^2, SO, SO^2, NSO_2R^{14}, etc.

Information Disclosure Statement

4. Applicant's Information Disclosure Statement, filed on 09/19/2005 has been acknowledged. Please refer to Applicant's copies of the 1449 submitted herewith.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In claims 35-36, it is recited a method for modulation of chemokine receptor activity in a mammal (claim 35) and a method of treating, ameliorating, controlling or reducing the risk of in inflammatory and immunoregulatory disorder or disease (claim 36), but the specification is not enabled for such a scope.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The scope of the claims is not adequately enabled solely based on the activity related to chemokine receptor activity provided in the specification. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is very broad. At page 3 of the specification, it is disclosed that chemokine receptors are useful in the prevention or treatment of certain inflammatory and

immunoregulatory disorders and diseases, allergic diseases, atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, asthma, autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. Applicants also disclose at page 3, "The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and composition in the prevention or treatment of such diseases in which chemokine receptors are involved. Test procedures and assays are provided in the specification at page 18-19 and it is concluded that the compounds of the following examples had activity in binding to the CCR-2 receptor with IC_{50} of less than about 1 μM, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced the instant claims. The disorders encompassed by the instant claims (i.e. inflammatory and immunoregulatory disorder or disease in general), some of which have been proven to be extremely difficult to treat. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

The claims are drawn to 'treating **inflammatory** disorder or disease in general ', however, there is magic bullet that can treat inflammatory disorder in general. Enablement for the scope of inflammation generally is not present. For a compound or genus to be effective against inflammatory disease or disorder generally is contrary to

medical science. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation

of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

Claim 36 is drawn to a method for treating, ameliorating, controlling or reducing the risk of an immunoregulatory disorder or disease, but the specification is not enabled for such scope. Immunology is the study of our protection from foreign macromolecules or invading organisms and our responses to them. These invaders include viruses, bacteria, protozoa or even larger parasites. In addition, we develop immune responses against our own proteins (and other molecules) in autoimmunity and against our own aberrant cells in tumor immunity. Our first line of defense against foreign organisms are

barrier tissues such as the skin that stop the entry of organism into our bodies. If, however, these barrier layers are penetrated, the body contains cells that respond rapidly to the presence of the invader. These cells include macrophages and neutrophils that engulf foreign organisms and kill them without the need for antibodies. Immediate challenge also comes from soluble molecules that deprive the invading organism of essential nutrients (such as iron) and from certain molecules that are found on the surfaces of epithelia, in secretions (such as tears and saliva) and in the blood stream. This form of immunity is the innate or non-specific immune system that is continually ready to respond to invasion.

A second line of defense is the specific or adaptive immune system which may take days to respond to a primary invasion (that is infection by an organism that has not hitherto been seen). In the specific immune system, we see the production of antibodies (soluble proteins that bind to foreign antigens) and cell-mediated responses in which specific cells recognize foreign pathogens and destroy them. In the case of viruses or tumors, this response is also vital to the recognition and destruction of virally-infected or tumorigenic cells. The response to a second round of infection is often more rapid than to the primary infection because of the activation of memory B and T cells. These signals may be proteins such as lymphokines which are produced by cells of the lymphoid system, cytokines and chemokines that are produced by other cells in an immune response, and which stimulate cells of the immune system.

The following diseases as shown below are examples of immunoregulatory disorders.

TYPE-I HYPERSENSITIVITY: IMMEDIATE. Mediated by IgE molecules binding to Fc-receptors on Mast Cells and Basophils.

- Examples:
    - Hay Fever, allergic rhinitis
    - Penicillin anaphylaxis.
    - Local anaphylaxis.
- **SENSITIZATION:** Initial formation of the IgE. Prior exposure to the allergen is required for an allergic reaction to happen later.
    - In atopic individuals, certain *allergens* promote the formation of IgE rather than IgG antibody.
        - **IL-4** promotes class switching to IgE.
        - IgE is normally only formed against parasites.
    - IgE binds to a **High-Affinity Fc-Receptor** on Tissue Mast Cells and Basophils.
        - Once bound, IgE sticks around for a long time. If it doesn't bind, it has a short half-life.
    - Once IgE is bound, the Mast Cells and Basophils are said to be *sensitized* and are subject to subsequent anaphylactic degranulation.
- **LOCALIZED ANAPHYLAXIS:** Allergic responses limited to a specific target organ.
    - **ATOPY**: The inherited tendency to manifest localized anaphylactic responses. Atopy is the property of being allergic.
    - EXAMPLES: Localized allergic reactions
        - **Asthma**: Allergic (IgE-mediated) Asthma differs from intrinsic Asthma. Allergic asthma is the anaphylactic response to airborne allergens in the lungs.
        - Hay Fever (Allergic Rhinitis)
    - PRIMARY SYMPTOMS OF ANAPHYLAXIS: See below for mediators
        - Bronchoconstriction

- Mediated by TXA_2, PAF

- Shock: Increased vascular permeability and vasodilation
  - Mediated by NO and Prostaglandins
- Vomiting (GI, urinary smooth muscle contraction)

- **IgE CROSS-LINKING and DEGRANULATION:** In secondary allergic response, cross-linking of antigen with IgE on Mast cells causes degranulation.
  - CROSS-LINK: Proper ratio of 2:1 (IgE:antigen) must occur before cross-linking leads to degranulation.
    - Second messenger is an alpha-adrenergic (IP_3/DAG) pathway, leading to increased Ca^{+2} which causes degranulation.
  - DEGRANULATION occurs as a result of Ca^{+2} influx and causes release of the following mediators from Mast Cells and Basophils:
    - **Histamine**: Vasoactive amine.
      - Effects:
        - Intense bronchial smooth muscle contraction
        - Increased vascular permeability
        - Increased secretion by nasal, bronchial, and gastric glands.
      - **H1-Receptors:** Induces contraction of GI and bronchial smooth muscle
      - **H2-Receptors:** Found on exocrine glands and on vasculature -- increased permeability and secretion.
    - **Serotonin** has effects similar to Histamine.
    - **Eosinophil and Neutrophil Chemotactic Factors (ECF, NCF):** Attract Eosinophils and Neutrophils for the late phase response.
    - Proteases generate complement split-products and cause bronchial mucus secretion.
    - **EICOSANOIDS:** PGD2, LTB4, so called "secondary mediators" because they are not derived from granules.
      - **LEUKOTRIENES:** Slow-acting substances of anaphylaxis.

- Extremely potent bronchoconstrictors.

- **PROSTAGLANDINS**

- Both are derived from **Arachidonic acid**, which is formed from **Phospholipase-A_2** in the membrane. The Phospholipase A_2 is activated by Ca^{+2} influx.

- **PLATELET-ACTIVATING FACTOR (PAF):**

- It is not derived from Arachidonic Acid.

- Effects:

- Platelet-aggregation and degranulation

- Bronchoconstriction

- Cytokines: **IL-1** and **TNF-alpha** are released by Mast Cells.

- **EOSINOPHILIA** is a common sign of a Type-I allergic reaction. They normally accumulate late in a Type-I response.

- Eosinophils normally mount attack against **parasites** and that's all.

- Eosinophils will bind directly to antibody-coated allergen (ADCC) via their Fc receptors for IgG and IgE.

- Eosinophils also release inflammatory mediators themselves, that aid in parasitic infections, but hurt in allergic responses:

- **Leukotrienes** (slow-reacting substances of anaphylaxis).

- **Major Basic Protein**

- **Eosinophil-Derived Neurotoxin**

- **Cationic Protein**

- **PAF**

- **ALLERGENS:** Non-parasitic antigens that are capable of inducing the release of IgE. These substances all have the potential to cause anaphylaxis in *atopic* persons.

- *Normally, IgE is only formed against parasitic infections.*

- Examples:

- DRUGS: Penicillin, Codeine, Vancomycin, Cephalosporin

        - Bee and Wasp venom
        - Ragweed
        - Various foods
- REGULATION OF TYPE-I RESPONSE: Generally promoted by **T_H2** cytokines.
    - T_H1 cells reduce the Type-I response.
    - T_H2 cells enhance the Type-I response, via IL-3, IL-4, IL-5, IL-10
    - **IL-4** is the most important promotor of anaphylaxis.

TYPE-II HYPERSENSITIVITY: ANTIBODY-DEPENDENT CYTOTOXIC HYPERSENSITIVITY. A reaction of soluble IgG, IgM antibody with membrane-bound antigen (usually autoantigen)

- Examples:
    - **ACUTE HEMOLYTIC ANEMIA** resulting from Blood-transfusion reactions: The ABO antigens are already present (if they are not self) because antibodies have been formed to normal gut flora, which happen to have polysaccharide antigens that mimic the RBC blood-groups.
        - PATHOPHYS: Transfusion reaction ------> Complement-mediated lysis of RBC's. Massive intravascular hemolysis. Reaction may be immediate or delayed.
        - SYMPTOMS: Fever, chills, nausea, hemoglobinuria, clotting.
    - **ERYTHROBLASTOSIS FETALIS** (Fetal reaction to maternal Rh antibody).
        - Pregnancy is at risk if Mother is **Rh^-** (and thus has Rh antibody) and has a baby with father who is **Rh^+**, thus the baby is Rh^+ and has Rh antigen.
            - First pregnancy is OK; the mother forms antibody against fetal blood during parturition, but it usually does not react with fetus.
            - Subsequent Pregnancies: The mother has *preformed antibodies*, and, if left untreated, they will react with fetal blood in-utero, resulting in fetal high immature RBC count (erythroblastosis).
    - Autoimmune Hemolytic Anemia.

- **COMPLEMENT:** IgG and IgM and activate Complement via Fc receptors on endothelial cells. Complement is then activated via Classical (antibody-dependent) pathway. Complement effects:
    - Cell Lysis through **MAC**. This accounts for hemolysis in certain kinds of hemolytic anemias.
    - **OPSONIZATION** via **C3b** which acts as an opsonin: phagocytic cells express **C3b-receptors** and can thus bind to targets. This also occurs in certain autoimmune hemolytic anemias.
- **Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC): Natural Killer Cells,** as well as macrophages and some PMN's have Fc-receptors and can thus attack IgG-coated target cells and lyse them. This process occurs without phagocytosis.
    - This may play a role in Hashimoto's Thyroiditis.

TYPE-III HYPERSENSITIVITY: IMMUNE-COMPLEX HYPERSENSITIVITY. Accumulation of immune-complexes, formed by soluble antibody and soluble antigen.

- Examples:
    - Systemic Lupus Erythematosus (SLE)
    - Rheumatoid Arthritis
    - Glomerulonephritis
    - Goodpasture's Syndrome
- **SERUM SICKNESS:** Horse or bovine serum can be injected into human's as an antidote to bee venom or snake bites. The foreign serum will then induce formation of immune-complexes, which elicit symptoms 6 to 8 days later.
    - SYMPTOMS: Fever, arthralgia, vasculitis, acute glomerulonephritis.
- **ARTHUS REACTION:** Experimental **vasculitis**, in which a localized injury is produced by immune complexes. Immune-complexes accumulate on vessel walls which activated complement ------> vascular endothelial lesions.
- **PPD TB SKIN TEST** is also an example of a delayed hypersensitivity reaction.

TYPE-IV HYPERSENSITIVITY: DELAYED-TYPE HYPERSENSITIVITY (DTH). Antibody-independent, cell-mediated response of T_C cells against antigen. Reaction is generally 24 to 72 hours after allergen exposure.

- Examples:
    - Poison Ivy, Contact Dermatitis

- Tuberculosis infections, and other intracellular parasites (where antibodies are inaccessible to them).
- Graft rejection.

- SENSITIZATION is required, just like Type-I response.
- ACTIVATION: **T_H1** cells recognize the antigen directly and release lymphokines in response to it. Mature, specific T_H1 cells proliferate in response to antigen presented by macrophages or B-Cells. They then release cytokines:
  - **IL-2** stimulates growth of more T_H cells in an autocrine fashion.
  - **IFN-gamma** powerfully activates **MACROPHAGES**.
    - This stimulates them for phagocytosis (ADCC, opsonization).
    - Increases their oxidative burst ------> reactive oxidative intermediates.
    - This also makes them produce more MHC-II molecules, which makes them yet better APC's.
  - In **GRANULOMATOUS REACTION**, the macrophages can further turn into **Epithelioid Cells** and **Giant Cells**, in order to fight indigestible material or intracellular parasites such as *mycobacterium tuberculosis*.
  - Cytotoxic Cells recognize antigens directly, and proliferate in response to it.
  - **Natural Killer (NK)** cells can also proliferate in Type-IV responses. They have Fc receptors and respond primarily to membrane glycoproteins, virus-infected cells, or tumor cells.

TOLERANCE: Active state of immunologic non-responsiveness to self.

- **TOLEROGEN:** A substance that induces tolerance. It shows specificity and memory, just like immunogens.
- Experimental Tolerance Induction:
  - Tolerance is induced more readily in immature cells than in mature cells.
  - EXPT: Take Strain-A mice at birth and inject them with Strain-B mice spleen cells.

        - As adults, the A-mice had tolerance to skin grafts B skin, because they were exposed to the B spleen cells during early development and thus perceived them as self.

    - Maintenance of tolerance depends on the persistence of antigen. *Tolerance does not last indefinitely!*

- Factors that promote tolerogenicity:

    - **Oral Tolerance:** Antigens introduced orally rend to promote tolerance.

        - Teleologically, this is probably because we ingest a lot of nutrients that are potentially antigenic. If it is nutritional food, then we should be tolerant of it immunologically.

    - Intravenous administration of antigen promotes tolerance more readily than subcutaneous administration.

    - High dosage of an antigen tend to induce tolerance. Also, extremely low doses may induce tolerance. Anything in between tends to induce immunity.

- B-Cells -vs- T-Cells: Both T and B cells are subject to clonal anergy and clonal deletion. But, T-Cells generally exhibit more tolerance than B-Cells.

    - Induction of T-Cell tolerance requires less antigen than that of B-Cells.

    - T-Cell tolerance is acquired sooner and lasts longer.

    - Loss of tolerance happens faster in B-Cells than in T-Cells.

- Theories of Tolerance Induction:

    - **CLONAL DELETION:** This occurs during negative selection in the thymus -- delete cells that respond with high affinity to self.

    - **CLONAL ANERGY:** Active state of unresponsiveness.

        - **Absence of Co-stimulatory Signal** promotes tolerance rather than immunity -- it leads to clonal anergy of B-Cell progeny.

        - Anergy can occur in mature, peripheral B-Cells.

        - Anergic cells express way less mIgM on their membranes, but about the same IgD.

THEORIES OF AUTOIMMUNITY: Autoimmune diseases have multiple etiologies.

- SEQUESTERED ANTIGENS: Freeing of sequestered antigens. Examples = anterior chamber of eye (lens uveitis), testis (autoimmune orchitis), myelin basic protein (MS).
- IMMUNE-COMPLEX INJURY: Autoimmunity induced by injury of immune-complexes.
- CO-STIMULATORY MOLECULES being inappropriately expressed can induce autoimmunity.
- INAPPROPRIATE EXPRESSION of HLA:
    - In IDDM, Pancreatic beta-Cells express too high levels of MHC-I and MHC-II.
    - Grave's Disease: similar finding
- CYTOKINE IMBALANCE: T_H1 activation over T_H2 can lead to autoimmune disease.
    - IL-2 is found in excess, plus too much IFN-gamma.
- ABNORMAL T-CELL FUNCTION: Lack of **suppressor T-Cells.** This theory has the most evidence supporting it.
- CROSS-REACTIVITY: Biological Mimicry with microbial antigens, as in **Rheumatic Heart Diseases**, in which antibodies against streptococcal antigens cross-react with myocardium.
- POLYCLONAL B-CELL ACTIVATION: Something stimulates anergic B-Cells to become active, usually non-specifically.
- FAILURE-TO-DELETE THEORY: Simple failure of thymic negative selection causes autoimmunity.

WITEBSKY'S POSTULATES: Experimental Autoimmune Encephalitis (EAE) is autoimmunity to Myelin Basic Protein in rats.

- Myelin Basic Protein is normally a sequestered antigen, protected by blood-brain barrier.
- If you experimentally expose rats to their own MBP, then they will show an immune response to it.
- This sequestered antigen could also be freed, however, by trauma, infection, etc.
- Once formed, the immunity can be transferred by a T-Cell clone to a recipient, and the same disease will be induced.
- **Multiple Sclerosis** = autoimmunity to Myelin Basic Protein

AUTOIMMUNE DISEASES: Most auto-immune diseases, for unknown reasons, occur predominantly in woman, sometimes by a margin of 10:1 or greater.

- **HASHIMOTO'S THYROIDITIS:** A combination of Type-II (organ-specific) and Type-IV (cell-mediated) auto-immune disease.
    - PATHOGENESIS: Type-II ADCC against thyroglobulin, and against thyroid peroxidase (microsomal bodies).
    - SYMPTOMS: **Goiter**, due to inflammatory infiltrates in the thyroid.
    - **HASHITOXICOSIS:** Severe hyperthyroidism found in this disease. This is often followed by destruction of thyroid tissue and hence severe hypothyroidism.
    - OTHER DISEASES: Many other autoimmune diseases are commonly associated with Thyroiditis: SLE, Rheumatoid Arthritis, Sjögren, Addison's, IDDM.
- **HEMOLYTIC ANEMIAS:** Complement mediated lysis or antibody mediated opsonization of red blood cells.
    - **WARM HEMOLYTIC ANEMIA:** IgG antibodies against Rh antigens.
    - **COLD HEMOLYTIC ANEMIA:** IgM antibodies specific for other RBC antigens (I and H).
        - Symptoms occur when blood is exposed to cold, such as extremities exposure to cold.
- **THROMBOCYTOPENIA:** Low platelet count. Autoimmunity against platelets is often found with autoimmune hemolytic anemias.
- **INSULIN-DEPENDENT DIABETES MELLITUS (IDDM):** Auto-immune attack against Insulin-secreting beta-Cells in pancreas.
    - The disease is a Type-IV cell mediated auto-immune disease.
- **PERNICIOUS ANEMIA:** Autoimmunity against **Intrinsic Factor (IF)** in Parietal Cells in the stomach.
    - No Intrinsic Factor ------> No absorption of B-12 in large intestine ------> hemolytic anemia.
- **GRAVE'S DISEASE:**
    - PATHOPHYS: Type-II autoimmune attack against TSH-receptors in the thyroid gland, resulting in over activation of them ------> Hyperthyroidism.

- This is a disease where an auto-antibody acts as an **Agonist**.
- The antibodies are called "Long Acting Thyroid Stimulating" (LATS) antibodies.

- **MYASTHENIA GRAVIS:** Type-II autoimmune attack against Nicotinic Acetylcholine receptors ------> block Ach-receptors ------> FFatigable Weakness.
  - This is a disease where an auto-antibody acts as an **Antagonist**.
- **GOODPASTURE'S SYNDROME:** Type-II Autoimmune attack against Collagen-IV basement membrane components.
  - SYMPTOMS: In Goodpasture's, the auto-antibodies attack primarily the **Glomerular Basement Membrane** and **Pulmonary basement membrane** ------> Renal Failure (**Glomerulonephritis**) and Pulmonary dysfunction.
    - Classic dual symptoms are therefore **hemoptysis** and **renal failure**.
  - PATHOPHYS: Complement split products build up as a result of the inflammatory response against basement membranes.
  - DIAGNOSIS: Immunofluorescence shows a linear array of immunofluorescence, as antibodies bind to basement membrane.
- **MULTIPLE SCLEROSIS (MS):** Autoimmune (probably Type-II) attack against Myelin Basic Protein, resulting demyelination of nerves.
  - Activated T-Cells are found in cerebrospinal fluid.
- **SYSTEMIC LUPUS ERYTHEMATOSUS (SLE):** Type-III Hypersensitivity in which immune complexes are formed against nuclear components in any lysed cells. This is the most common systemic auto-immune disease.
- **SJÖGREN SYNDROME:** Also predominantly Type-III Autoimmune disorder characterized by **sicca** (dry eyes) and **xerostomia** (dry mouth). Second most common connective tissue disorder, after SLE.
  - **Rheumatoid Factor** is commonly found, whether or not they have Rheumatoid Arthritis.
  - Associated with a 4-fold increased risk for **malignant lymphoma**.
- **RHEUMATOID ARTHRITIS:** Autoimmune inflammation of joints.
  - **Rheumatoid Factor:** Antibody against the Fc portion of IgG, such that it forms an IgG complex which then deposits in joints.

- **IgM-IgG** Complex is the most common to form.

- **CONTACT DERMATITIS:** Type-IV delayed hypersensitivity. Poison Ivy.

IMMUNE DEFICIENCY DISEASES: Most congenital immunodeficiency diseases are X-linked and thus occur only in males.

- PHAGOCYTIC IMMUNE DEFICIENCIES: As a group these diseases lead to recurrent bacterial and fungal infections.
  - **CONGENITAL NEUTROPENIA:**
    - Stem cells are present but don't mature.
    - Deficiency in **G-CSF**, such that granulocytes don't mature.
    - SYMPTOMS: Infantile bacterial infections.
  - **LEUKOCYTE ADHESION DEFECT (LAD):** Inability for neutrophils to extravasate due to inability to bind to endothelia.
    - PATHOPHYSIOLOGY:
      - **Complement Receptors, CR3 and CR4** deficient, or,
      - **LFA-1** could be deficient, resulting in no adhesion to ICAM-1 in endothelia.
  - **CHRONIC GRANULOMATOUS DISEASE (CGD):** X-Linked recessive
    - PATHOPHYS: Cytochrome-B deficiency resulting in **no NADPH Oxidase ------> No Oxidative Burst**, because of inability to recycle NADP.
      - Impairs the killing ability of neutrophils.
      - Catalase-negative bacteria can still be killed by the defective neutrophils, because they form their own H_2O_2 in bacterial metabolism, and they don't have the catalase to break it down.
    - SYMPTOMS: Granulomas all over the place.
  - **MYELOPEROXIDASE DEFICIENCY:**
- HUMORAL (B-CELL) DEFICIENCIES: Usually subject to recurrent bacterial infections, but display normal immunity against viral and fungal infections.
  - **CONGENITAL X-LINKED HYPOGAMMAGLOBULINEMIA (XLA) (BRUTON'S DISEASE):** Deficient in all immunoglobulins.

- PATHOPHYS: Caused by a defect in the early maturation B-Cells. Pre-B Cells are detected but cannot mature.
    - Appears to be a specific defect in the V-D-J gene-rearrangement machinery.
- Age of Onset: Infantile about 6 months, after maternal passive immunity has worn off.

- **COMMON VARIABLE IMMUNODEFICIENCY**: Late-onset Hypogammaglobulinemia (deficient IgG).
    - EPIDEMIOLOGY:
        - Age of Onset: Adult, 15-30 years.
        - Affects both men and women equally.
    - SYMPTOMS: Recurrent pyogenic bacterial infections.
    - PATHOPHYS: Appears to be in the activation of mature B-Cells to antibody-secreting Plasma Cells.

- **SELECTIVE IGA DEFICIENCY:** Most common of immunodeficiencies. B-Cell count is normal, but IgA is not synthesized or secreted. Could be a problem with class-switching or with the secretory pathway.
    - Symptoms:
        - Recurrent or opportunistic GI-tract and respiratory infections.
        - Increase incidence of allergic infections.
- **TRANSIENT HYPOGAMMAGLOBULINEMIA OF INFANCY**

- T-CELL DEFICIENCIES: Increased susceptibility to viral and protozoal infections, and to intracellular pathogens such as *mycobacterium tuberculosis, candida albicans,* and *pneumocystis carinii.*
    - **DIGEORGE SYNDROME:** Congenital malformation of 3rd and 4th Brachial Pouches, resulting in no formation of Thymus.
        - SYMPTOMS:

- Patient will present with severe **hypocalcemia** due to hypoparathyroidism (Parathyroid does not form normally).
- Concurrent cardiac defects are common, and the most common cause of death.
- TREATMENT: Grafting of fetal thymus tissue. Must use fetal tissue younger than 14 months to prevent Graft -vs- Host Disease.

- **ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS):** Infection of CD4 cells by HIV retrovirus.
  - Common Complications: Opportunistic infections. Of course this list is not complete.
    - **Persistent Generalized Lymphadenopathy**: Common early symptom. Persistent enlargement of lymph nodes with no apparent cause.
    - **Kaposi Sarcoma** is a common skin cancer that occurs all over the body in AIDS and rapidly metastasizes.
    - **Pneumocystis Carinii** is an opportunistic pathogen that frequently causes pneumonia in immunocompromised patients.
    - **Cytomegalovirus**
    - **Toxoplasmosis** occurs in the brain where it forms lesions that are evident on MRI. Toxoplasmosis occurs in normal people, too, but it doesn't form the lesion because our immunity can quickly wipe it out.
    - **Candida** infections.
  - **gp120** is the name of the viral-coat protein, which recognizes CD4 receptors on T_H cells in order to gain entry into the cells.

- COMBINED IMMUNODEFICIENCIES:
  - **BARE LYMPHOCYTE SYNDROME:** Deficiency in expression of MHC molecules resulting in impaired antigen presentation.
    - Types:
      - Type-I: Defective MHC-I
      - Type-II: Defective MHC-II.

- Type-III: Both are defective.

- **SEVERE COMBINED IMMUNODEFICIENCY (SCID):** Absence of both T and B-Cells. Onset at 6 months.
  - **Adenosine Deaminase Deficiency** is usually the cause in autosomal-recessive SCID (there is also an X-linked form). Deficiency of ADA leads to accumulation of deoxyadenosine and its derivatives (e.g., deoxy-ATP), which are toxic to immature lymphocytes.

- **WISKOTT-ALDRICH SYNDROME:** Rare X-linked, cause unknown.
  - PATHOPHYS: It is a complete failure to produce antibodies against polysaccharides. Absence of adhesio protein **CD43**.
  - FINDINGS: Normal IgG, low IgM, elevated IgA and IgE.

- COMPLEMENT DEFICIENCIES: See complement section.
- **CHRONIC MUCOCUTANEOUS CANDIDIASIS:** Specific immunodeficiency against Candida fungi and nothing else.

As shown above, immunoregulatory disorders are very broad in nature. Applicants claim to treat immunoregulatory disorder in general is not enabled.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

It is recommended that applicants amend claim 35 as follows: A method for modulation of chemokine receptor CCR-2 activity *in vitro* which comprises the administration of an effective amount of the compound of claim 1".

In regard to claim 36, it is recommended that applicants delete claim 36 to overcome this rejection.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4,10-13,17-19 and 22-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a. Claim 1 or claims depend thereon are rejected because the term "heterocycle" is indefinite. What is the size of the ring? What is the number and nature of the heteroatoms? Can the ring be fused or spiroconnected to another ring, and if so, what kind of ring? Can the ring be bridged? Unsaturated? Cf *In re Wiggins*, 179 USPQ 421, 423.

b. In claim 1, the phrase "R3 is nothing, O, or hydrogen, when Z bonded to R3 is nitrogen" is not clear. How can oxygen (O) be a substituent when D = C? If O is

substituted on C, the molecule as a whole would be charged. Like wise, what does it mean R3 = nothing when D is C? Applicants have to fix this problem elsewhere in the claims.

c. Claim 18 is rejected because it is improperly dependent from claim 16. Claim 18 recite "D is carbon", but claim 16 there is no mention of "D is carbon" in claim 16.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kahsay Habte
Primary Examiner
Art Unit 1624

KH
September 13, 2007